II. Claim Objection

The Examiner objected to Claim 1 because it did not begin with an indefinite article. Accordingly, Applicants have inserted the indefinite article "a" before the term "sequence" in Claim 1. The Examiner objected to Claim 26 because the phrase "wherein said retroelements comprise cis-acting region" lacked the indefinite article "a" before the term "cis-acting." Claim 26 has been deleted. Applicants respectfully request that the objections to Claims 1 and 26 be withdrawn.

III. Rejection Under 35 U.S.C. § 112, Second Paragraph

The Examiner rejected Claims 1 and 32-35 under the second paragraph of 35 U.S.C. § 112, asserting that the claims were indefinite. The Examiner rejected Claim 1 because the word "preferably" renders the phrase "preferably a single recognition site which can be recognized by a recombinase" vague and renders the claim indefinite because it is unclear whether the limitations that follow are part of the claimed invention. To address this rejection, Claim 1 has been amended to delete the phrase "preferably a single recognition site which can be recognized by a recombinase." In place of the deleted phrase is the newly added Claim 41, which depends from Claim 1 and recites a single recognition site that can be recognized by a recombinase.

The Examiner also rejected Claim 1 because the phrase "[s]equence of synthetic or natural retroelements, in particular of retroviral DNA" recites both a

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

broad and an included, narrower, limitation. To address this rejection, Claim 1 has been amended to delete the phrase "in particular of retroviral DNA." In place of the deleted phrase is the newly added Claim 42, which depends from Claim 1 and recites a retroelement sequence comprised of retroviral DNA.

The Examiner rejected claims 32-35, which recite a "recognition site," because Claim 25, from which they depend, recites a "recognition sequence." Claim 25 has been amended to recite a "said recognition site" for the elimination of proviral sequences. This recitation is supported in the specification. At page 7, lines 20-33, Applicants describe the "recognition site" loxP, which is employed to eliminate proviral sequences. The term "site" is also supported on page 12, lines 3-18, which describe a loxP "recognition site," and page 14, lines 3-6, which describe a "proviral integration site." Accordingly, Applicants respectfully request that the rejection of Claims 1 and 32-35 be withdrawn.

IV. Rejection Under 35 U.S.C. § 112, First Paragraph

The Examiner rejected Claim 39 under the first paragraph of 35 U.S.C. § 112, asserting that it contained subject matter, which was not described in the specification, in such a way as to enable one skilled in the art to make and/or use the invention. Specifically, the Examiner indicated that the specification was not enabling without either evidence that the plasmid with Accession Number I-1599 is known and readily available to the public, or evidence of the deposit of the biological material.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Applicants respectfully traverse this ground for rejection with a Deposit Declaration, and copies of the Application Form and Authenticity Check executed by the Collection Nationale De Cultures De Microorganismes (C.N.C.M.). The attached Deposit Declaration is signed by the Assignee, and states that the plasmid was deposited with the C.N.C.M., which acquired international authority of deposit under the treaty of Budapest on August 31, 1984. The C.N.C.M. is listed as an acceptable International Depository Authority in § 2405 of the MPEP, pages 2400-7 to 2400-10. The attached Deposit Declaration also states that all restrictions on the public availability of the pM Cre Lox PL plasmid having Accession Number I-1599 will be irrevocably removed no later than upon the issuance of a patent. It further states that the Assignee will replace the deposit if the depository cannot dispense viable samples during the period that extends thirty (30) years from the date of the deposit, or the period of the enforceable life of the patent, or the period of five years after the last public request for the deposit, whichever period is longest.

Applicants have amended Claim 39 to spell "Accession" correctly.

V. Rejection For Double Patenting

Claims 25-26, 29-32, 37, and 40 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,200,800. Applicants file herewith a Terminal

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Disclaimer pursuant to 37 C.F.R. 1.321. Accordingly, the rejection may be withdrawn.

VI. Rejection Under 35 U.S.C. § 102(e)

The Examiner rejected Claims 1, 25-26, 29-32, 36-37, and 40 under 35 U.S.C. § 102(e), asserting they are anticipated by Anderson's U.S. Patent No. 5,629,159. Applicants respectfully traverse this ground for rejection and request reconsideration for the following reasons.

Anderson provides a method for introducing an immortalizing oncogene into a cell, proliferating the cell *in vitro*, excising the oncogene, and then performing gene therapy. Anderson's method recites vectors that express sequences of interest within the cis-acting region of the virus, and include control elements, selectable markers, and 3' and 5' LTR elements. The exogenous nucleotides are not inserted within the 3' or 5' LTR elements. The inserted exogenous sequences are distinct from the 3' or 5' LTR elements. This distinction is illustrated in Figures 1 and 2, in which the LTRs are depicted as elements, which are discrete and separate from the control elements, the selectable markers, and the other elements of the vector. Furthermore, Anderson describes selectable markers that are driven by "promoters internal to the LTR," further demonstrating the distinction between the LTRs and other components of the vectors. Anderson, page 7, lines 53-56.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Applicant's invention differs from Anderson's vector by placing an insertion sequence within the 3' LTR or the 5' LTR region. Claims 25 and 28 have been amended to recite an insertion sequence located in an LTR region. Amended claim 25 recites "an insertion sequence located in the 3' and/or the 5' LTR region. It is supported by the specification, which discloses that the "insertion sequence is incorporated into a cis-acting region, more particularly in the 3' LTR or the 5' LTR region and preferably in the U3 region of the 3' LTR or the U5 region of the 5' LTR of this retroviral sequence." Specification, page 2, lines 31-34. Claim 28 recites that the retroelements of the invention comprise a U3 region of a 3' LTR and a U5 region of a 5' LTR. The sequence of interest and the recognition sequence are "incorporated into" the U3 or U5 regions. Amended Claim 28 is supported by the specification, which discloses that the nucleotide sequence of interest is introduced "into the U3 region of 3' LTR." Specification, page 7, lines 34-37. Example 1a, illustrated by Figure 1, discloses a sequence of interest inserted into the U3 region of an LTR. Specification, page 12, lines 12-13. The specification also discloses that retroelements can be inserted into the U5 region of the 5' LTR. Specification, page 8, line 2. Accordingly, Anderson can not suggest or teach the claimed invention, and Applicants respectfully request that this rejection be withdrawn.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

VII. Rejection Under 35 U.S.C. § 103

A. Anderson in View of Sun, et al.

In the Office Action of August 16, 2002, the Examiner rejected Claims 1, 25-38, and 40 under 35 U.S.C. § 103(a) as unpatentable over Anderson in view of Sun et al. The Examiner also cited "Taylor et al." in line 2 of paragraph 14, but did not make further reference to Taylor, nor is there a reference on file by Taylor disclosed by Applicants or the Examiner.

The Examiner asserted that Anderson discloses a retroviral vector comprising a stop sequence that prevents the translation of a selectable marker. Anderson Column 7 lines 53-58. The Examiner concluded that it would have been obvious to replace the stop sequence with an antisense or ribozyme sequence to the selectable marker, either of which would inhibit translation of the selectable marker. The Examiner reasoned that a skilled artisan would have been motivated to make that modification because Anderson's stop sequence is functionally equivalent to an antisense or ribozyme sequence. The Examiner further asserted that Figure 1 of Sun et al. provides guidance for such a modification because it directs an artisan to design retroviral constructs with antisense or ribozyme sequences inserted between two LTR retroelements.

Applicants respectfully traverse this ground for rejection and request reconsideration. The combination of Anderson with Sun et al. to place an antisense or ribozyme sequence between a 3' LTR and a 5' LTR does not result in Applicants' invention. Anderson's disclosure of a vector with a sequence that

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

stops translation of a selectable marker gene combined with Sun's disclosure that antisense and ribozyme sequences can be placed between a 3' LTR and a 5' LTR do not, when combined, describe Applicants' invention. Sun's disclosure places antisense and ribozyme sequences between a discrete 3' LTR and a discrete 5' LTR. Applicant claims an insertion sequence located within 3' or 5' LTR regions, not between discrete 3' and 5' LTR regions.

Furthermore, Anderson's stop sequence is present in order to prevent the translation of a selectable marker. Anderson's method utilizes a negative selection marker to excise an immortalized gene; failure to do so would introduce an oncogene into a patient. Anderson Column 5 lines 36-38. In contrast, Applicant's invention does not require a negative selection marker to excise an immortalized gene. In the absence of such a requirement, a skilled artisan would not have been motivated to modify Anderson's stop sequence in any way, including by placing antisense RNA or a ribozyme sequence between a 3' LTR and a 5' LTR. Because Anderson, in view of Sun, et al., does not disclose Applicants' invention, and in the absence of motivation to combine the cited references, Applicants respectfully request that this rejection be withdrawn.

B. Anderson's Figure 6A in View of Anderson's Figure 1A

The Examiner further asserted that it would have been obvious to one of ordinary skill to modify the teachings of Anderson to design a retroviral vector with a nucleotide sequence coding for a recombinase that is situated between the 5' LTR and the 3' LTR. The Examiner supported this conclusion by

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

reasoning that incorporating Anderson's inducible promoter linked to a recombinase gene, shown in Figure 6A, into his construct of Figure 1A, which teaches a removable oncogene placed between two LTRs, renders Applicants' invention obvious. Anderson's inducible promoter and recombinase gene are inserted after the second selection marker, which is located between the 5' LTR and the 3' LTR. It is not located within either the 5' or the 3' LTR.

Incorporating Anderson's recombinase linked to an inducible promoter into his construct of a removable oncogene between two LTRs would not result in Applicants' invention. As described above, Applicant's insertion sequences are situated within the 3' LTR, the 5' LTR or both, not between discrete LTRs, as disclosed and depicted by Anderson. Thus, Applicants respectfully request that this ground for rejection be withdrawn.

C. Guild et al., in view of Enquist et al., and Anderson

In the Office Action of February 22, 2002, the Examiner rejected Claims 25-38 and 40 as *prima facie* obvious under 35 U.S.C. § 103 over Guild in view of Enquist et al. and Anderson. The Examiner asserted that one of ordinary skill in the art would have been motivated to combine the teachings of Guild et al., namely, that of a retroviral vector with an insertion site for a gene of interest, with Enquist et al.'s teaching of the utility of modifying vectors so that sequences of interest could be inserted and removed. The Examiner reasoned that an ordinarily skilled artisan would have been further motivated to combine the teachings of Anderson to encode the recombinase into the vector, and use it to

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

excise sequences that are rendered unnecessary when the vector integrates into the host DNA. Applicants respectfully traverse this ground for rejection.

The Examiner first cited Guild at page 16, lines 20-24, which teaches that the gene of interest is cloned into a site "just distal to the 5' LTR." Thus, in Guild's disclosure, the spatial relationship of the gene of interest and the 5' LTR is such that they are discrete entities, and the gene of interest is distal to the 5' LTR. In contrast, Applicants claim an insertion sequence, comprising a gene of interest, that is within the 5'LTR. The Examiner further states that Enquist provides the desirability of using recombination as a means of modifying retroviral vectors. However, Enquist's disclosure is limited to DNA viruses, and does not apply to retroviruses, which are RNA viruses. Enquist provides a process for inserting heterologous DNA into the "DNA of DNA-containing animal viruses." Enquist et al. page 3, lines 18-19. Finally, all of Enquist's cre-mediated recombination is performed *in vitro*. Applicants' vector recombines only *in vivo*, within the organism receiving the vector of the invention. Therefore, Enquist does not teach the desirability of using recombination as a means of modifying retroviral vectors. It teaches a method for producing selectable vectors *in vitro* in a DNA viral system. The primary reference that forms the basis for this rejection does not read on the claimed invention. Thus, Applicants respectfully request that this ground for rejection be withdrawn.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

VI. Conclusion

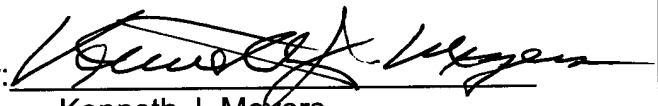
Applicants respectfully request the reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON,
FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: February 14, 2003

By: 
Kenneth J. Meyers
Reg. No. 25,146

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

Appendix

The specification, and Claims 1, 25, and 28 have been amended as follows. Claims 26 and 27 have been deleted. Claims 41-43 have been added.

IN THE SPECIFICATION:

Please amend Example 4a of the pending specification to read as follows:

Example 4 - Construction of the retroviral vector pMcreloxPL and transfection of cell lines

a) Construction of the ~~pMcreloxPL~~ XL-I Blue pM Crelox PL plasmid

The structure of the retrovirus used in the present example is illustrated in Fig. 3a. pMCreloxPL results from the insertion of the 1.3 kbp *cre* gene fused with a nuclear localization of the large T antigen of the simian virus 40 between the two LTR of the pMloxPL plasmid. The *cre* gene is under the transcriptional control of the promoter of the thymidine kinase gene (tk) of the herpès simplex virus flanked by a duplication of the enhancer at a distance of the polyoma mutant virus PYF441 with linkers at the PstI site of pMloxPL. The Cre sequence is in the same orientation as the viral genome. The XL-I Blue pM Crelox PL ~~pMcreloxPL~~ plasmid was deposited with the CNCM on 13 June 1995 under No.I-1599.

1. (Amended) A Ssequence of retroviral DNA comprising synthetic or natural retroelements~~, in particular of retroviral DNA, characterized in that it~~ and comprisinges an insertion sequence ~~incorporated in a region~~ which can be transferred into a target cell and integrated into a recombinant provirus when said target cell is infected by a retrovirus comprising said sequence; ~~of retroelements,~~

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

said ~~insertion~~ sequence comprises~~ing~~ a nucleotide sequence of interest which can be integrated into the genome of a target cell, ~~as well as~~ a recognition sequence~~, preferably a single recognition sequence which can be recognized by a recombinase~~, and a 3' and/or 5' LTR region.

25. (Amended) A nucleic acid molecule comprising

retroelements that comprise a recombinant provirus when a target cell is infected by a retrovirus containing said retroelements; said retroelements comprise

an insertion sequence located in the 3' and/or the 5' LTR region; said insertion sequence comprises

a nucleotide sequence of interest, which can be expressed in the target cell and which can be transferred with said retroelements into the target cell and integrated into the recombinant provirus; and

a recognition ~~sequence~~ site for the elimination of proviral sequences in the recombinant provirus, which are not necessary for expression of the nucleotide sequence of interest in the target cell after integration of the recombinant provirus into the target cell.

26. (Deleted) ~~The nucleic acid molecule as claimed in Claim 25, wherein said retroelements comprise cis-acting region and the nucleotide sequence of interest is incorporated into the cis-acting region.~~

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

27. (Deleted) ~~The nucleic acid molecule as claimed in Claim 25, wherein said retroelements comprise a 3' LTR or a 5' LTR region and the nucleotide sequence of interest is incorporated into the 3' LTR or 5' LTR region.~~

28. (Amended) The nucleic acid molecule as claimed in Claim 25, wherein the retroelements comprise a U3 region of a 3' LTR, a U5 region of a 5' LTR, and an R region, and the ~~nucleotide~~ sequence of interest ~~is~~ and the recognition sequence are incorporated into one of said regions.

39. (Amended) The nucleic acid molecule as claimed in Claim 25, which is contained in a plasmid deposited under C.N.C.M. ~~Assession~~ Accession No. I-1599.

41. (New) The nucleic acid molecule as claimed in Claim 1, wherein the recognition sequence is a single recognition sequence that can be recognized by a recombinase.

42. (New) The nucleic acid molecule as claimed in Claim 1, wherein the sequence is comprised of retroviral DNA.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com

43. (New) The nucleic acid molecule as claimed in Claim 1, wherein the retroelements comprise a U3 region of a 3' LTR, a U5 region of a 5' LTR, and an R region, and the sequence of interest and the recognition sequence are incorporated into one of said regions.

44. (New) The nucleic acid molecule as claimed in claim 41, wherein said retroelements comprise U3 of 3' LTR and/or U5 of 5' LTR and the insertion sequence is incorporated into U3 and/or U5.

45. (New) The nucleic acid molecule as claimed in claim 28, wherein said retroelements comprise U3 of 3' LTR and/or U5 of 5' LTR and the sequence of interest and the recognition sequence are incorporated into U3 and/or U5.

FINNEGAN
HENDERSON
FARABOW
GARRETT &
DUNNER LLP

1300 I Street, NW
Washington, DC 20005
202.408.4000
Fax 202.408.4400
www.finnegan.com